IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

REQUEST FOR FILING APPLICATION
Under Rule 53(a), (b) & (f)
(No Filing Fee or Oath/Declaration)
(Do NOT use for Provisional or PCT Applications)
Use for Design or Utility Applications

PATENT APPLICATION

RULE 53(f) NO DECLARATION

Assistant Commissioner of Patents
and Trademarks
Washington, DC 20231

Atty. Dkt. PM 264671 M# | 99/06 PH/De Client Ref

Date: March 10, 2000

Sir:

1. This is a Request for filing a new Patent Application(☐ Design ☒ Utility) entitled:

2. (Complete) Title: METHOD FOR A PROGRAMMED CONTROLLED OVARIAN STIMULATION PROTOCOL

without a filing fee or Oath/Declaration but for which is enclosed the following:

3. ☐ Abstract _____ page(s).

4. 9 Pages of Specification (only spec. and claims); 5. ☐ Specification in non-English language

6. 24 Numbered claim(s); and

7. ☐ _____ sheet(s) per set: ☐ 1 set informal; 8. ☐ formal of size: ☐ A4 ☐ 11" Drawings:

9. **DOMESTIC/INTERNATIONAL** priority is claimed under 35 USC 119(e)/120/365(c) based on the following provisional, nonprovisional and/or PCT international application(s):

Application No.	Filing Date	Application No.	Filing Date
(1) 60/127,241	March 31, 1999	(2) 60/131,632	April 28, 1999
(3)		(4)	
(5)		(6)	

10. **FOREIGN** priority is claimed under 35 USC 119(a)-(d)/365(b) based on filing in _____

Application No.	Filing Date	Application No.	Filing Date
(1)		(2)	
(3)		(4)	
(5)		(6)	

11. _____ (No.) Certified copy (copies): ☐ attached; ☐ previously filed (date) _____ in U.S. Application No. / _____ filed on _____

12. ☐ This is a reissue of Patent No. _____

13. ☐ See top first page re prior Provisional, National, International application(s) (X box only if info is there and do not complete corresponding item 14 or 15.)

14. ☐ **Amend the specification** by inserting before the first line -- This is a ☐ Continuation-in-Part ☐ Divisional ☐ Continuation ☐ Substitute Application (MPEP 201.09) of:

14(a) ☐ National Appln. No. / _____ filed .- - (M#)

14(b) ☐ International Appln. No. PCT/ _____ filed _____ which designated the U.S. - -

15. ☒ **Amend the specification** by inserting before the first line: --This application claims the benefit of U.S. Provisional Applications No. 60/127,241, filed March 31, 1999, and 60/131,632, filed April 28, 1999.--

16. Extension to date: ☐ concurrently filed ☐ not needed ☐ previously filed

17. ☐ Prior application is assigned to

by Assignment recorded _____ Reel _____ Frame _____

18. ☒ **Attached: Preliminary Amendment**

19. This application is made by the following named inventor(s) **(Double check instructions for accuracy.):**

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Residence			
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Residence			
	City	State/Foreign Country	Country of Citizenship
Post Office Address			
(include Zip Code)			

(5) Inventor			
	First	Middle Initial	Family Name
Residence			
	City	State/Foreign Country	Country of Citizenship
Post Office Address			
(include Zip Code)			

20. NOTE: FOR ADDITIONAL INVENTORS, check box ☐
and attach sheet with same information regarding additional inventors.

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NOTE: File in duplicate with 2 post card receipts (PAT-103) & attachments

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of ENGEL et al.

Application No.: Not Assigned — Group Art Unit: Not Assigned

Filed: March 10, 2000 — Examiner: Not Assigned

For: Method for a Programmed Controlled Ovarian Stimulation Protocol

* * * * *

March 10, 2000

PRELIMINARY AMENDMENT

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to examination of the above-referenced application, please enter the following amendments.

IN THE CLAIMS:

Please amend claim 1 as follows:

1. (Amended) In the method of therapeutic management of infertility by programming of controlled ovarian stimulation (COS) and assisted reproductive procedures (ART) the improvement consisting of

a) suppression of premature ovulation with an LHRH-antagonist in controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) with multiple follicle and oocyte development

b) programming the start of controlled ovarian stimulation (COS) by the administration of progestogen [-] only - or alternatively combined oral contraceptive preparations

c) exogenous stimulation of the ovarian follicle growth

d) ovulation induction with HCG, native LHRH, LHRH-agonists or recombinant [FSH] LH

e) application of assisted reproduction techniques, especially of IVF, ICSI, GIFT, ZIFT or by intrauterine insemination by sperm injection.

Early and favorable consideration of the application is respectfully requested.

Respectfully submitted,

PILLSBURY MADISON & SUTRO LLP

By _____

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APPLICATION UNDER UNITED STATES PATENT LAWS

Atty. Dkt. No. PM 264671
(M#)

Invention: METHOD FOR A PROGRAMMED CONTROLLED OVARIAN STIMULATION PROTOCOL

Inventor (s): Jürgen ENGEL
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This is a:

- ☐ Provisional Application
- ☒ Regular Utility Application
- ☐ Continuing Application
- ☐ PCT National Phase Application
- ☐ Design Application
- ☐ Reissue Application
- ☐ Plant Application
- ☐ Substitute Specification
  Sub. Spec Filed _____
  in App. No. / _____

SPECIFICATION

Method for a programmed controlled ovarian stimulation protocol

Field of Invention

Women are fertile for a limited time only. Unwanted childlessness occurs in one of 10 couples. The reason for unfulfilled wish for children is related to female factors, e. g. blocked or missing tubes, polycystic ovary disease, or to male factors, e. g. insufficient sperm motility.

To overcome this problem, female partners of infertile couples undergo ovarian stimulation with gonadotropins like HMG (human menopausal gonadotropin), FSH (follicle stimulating hormone) or by the antioestrogen clomiphene and gonadotropins. This therapy stimulates the growth of a cohort of 6 – 12 follicles and oocytes to guarantee the fertilisation of sufficient oocytes by highly specified laboratory technologies. During this procedure a premature ovulation indicated by an LH and progesterone surge is prevented by the administration of LHRH-analogues, either by LHRH-antagonists or by LHRH-agonists.

Background Information and Prior Art

According to the known treatment protocols HMG is given on day 2 of the menstruation cycle. A single or multiple dose of 0,25mg to 5mg of LHRH antagonist Cetrorelix was administered to prevent LH surges on day 5 until and including the day of ovulation induction with HCG. (Hum. Reprod. 1994 May;9(5):788-91, Hum. Reprod. 1995 Jun;10(6):1382-6, Fertil. Steril. 1997;67:917-22, Hum. Reprod. 1998 Sep;13(9)2411-4)

In the PCT application W0 98/58657 the LHRH antagonist ganirelix in an amount of 0,125 -1 mg is administered in the method to prevent premature LH surges in women undergoing controlled ovarian hyperstimulation in combination with exogeneous

FSH.

The EP 161 063 also teaches the use of a gonadotropin releasing hormone antagonist to prepare a pharmaceutical composition comprising a gonadotropin selected from HMG and FSH in the treatment of female infertility to suppress estrogen variability, in which treatment the antagonist composition is administered in an effective amount cojointly with the gonadotropin composition.

Usually for controlled induction of ovulation and final follicle maturation HCG (human chorionic gonadotropin) is given. 36 hours thereafter oocytes are picked up (OPU) by transvaginal or laparoscopic follicle puncture.

For the fertilisation of multiple oocytes by the sperms of the male partner assisted reproductive techniques (ART) are applied like IVF (in-vitro-fertilisation), ICSI (intracytoplasmic sperm injection), GIFT (gamete intra-Fallopian transfer) or ZIFT (zygote intra-Fallopian transfer) in highly specialized laboratories on the day of OPU.

Normally, two to four days after extracorporeal fertilization embryo transfer is performed by the replacement of several embryos into the cavum uteri to obtain pregnancy.

As many follicles develop following controlled ovarian stimulation therapy (COS) ovarian enlargement occurs and many oocytes are picked up. Therefore, oocyte pick up procedures have to be done in the operating theatre and with the application of general or regional anesthesia.

Assisted reproductive techniques are carried out in highly specialized laboratories by qualified personnel thereafter.

Preferably, these procedures have to be included into the routine operating theatre plans from Mondays to Fridays. The performance of oocyte pick up as well as of embryo transfer on weekends or holidays is avoided due to lack of enough qualified personnel on duty in most clinics. Furthermore, some hospitals undertake these

procedures only on a few days each month in order to have the oocyte pick up and fertilization procedures performed by a highly specialized serviceteam to increase the number of oocytes obtained as well as the fertilization rates and the number of good quality embryos. Therefore, programmed ovarian stimulation protocols are applied.

Object of the Invention

The present invention especially relates to the improvement of the method of programming of ovarian stimulation procedures, i. e. the administration of LHRH-antagonists in controlled ovarian stimulation where the start of menstrual cycle and ovarian stimulation was programmed.

Summary of the Invention

In a controlled ovarian stimulation procedure conducted with an LHRH–antagonist for the prevention of premature ovulation, gonadotropin injection is started at cycle day one to three of a menstrual cycle and is continued until the day of HCG when enough big follicles have developed.
The LHRH–antagonist is given at the days of risk of premature ovulation.
The duration of ovarian stimulation takes normally ten days in these treatment cycles.

In order to perform oocyte pick up and fertilization procedures during Mondays to Fridays the start of a menstrual cycle and of COS are programmed.
For the programming of the start of the menstrual cycle and of controlled ovarian stimulation procedures oral contraceptives or progestogen-only containing preparations are given in the follicular phase, preferably starting at menstrual cycle day 1 or 2 , or in the late luteal phase of the previous menstrual cycle.
The LHRH antagonist Cetrorelix was also used successfully for this purpose previously when 1mg were given in the luteal phase and luteal regression was obtained and menses started 2 to 4 days later.
The duration of oral contraceptive or progestogen administration will be a minimum of ten up to a maximum of 25 days. Intake of the last tablet will preferably be on a

Monday to Thursday to obtain start of menstrual bleeding and of ovarian stimulation therapy on Fridays to Mondays. Thereafter, oocyte pick up and further ART procedures can be scheduled and undertaken on Mondays to Thursdays.

The in a controlled ovarian stimulation procedure applied LHRH–antagonist for the prevention of premature ovulation can be for instance cetrorelix, teverelix, ganirelix antide or abarelix.

It is further in scope of the invention that the programming of COS and ART procedures is performed by oral administration of progestogen preparations, ethinylestradiol and progestogen, combined mono- bi- and triphasic contraceptive preparations containing contraceptive preparations, mestranol and progestogen, as well as by subcutaneous injection of LHRH antagonists.

The LHRH antagonists may be cetrorelix, teverelix, ganirelix, antide or abarelix and should be administered during the luteal phase in a dosage of 0,5 mg to 10 mg .

The ovarian stimulation is performed by administration of urinary or recombinant FSH or HMG, with or without recombinant LH and with antioestrogens as for example clomiphene also with a combination of antioestrogens as for example clomiphene with gonadotropins.

Example

Material and methods

A total of 30 patients, 15 from each German study center was enrolled for one treatment cycle. In the pre-treatment cycle , each patient received monophasic oral contraceptive(OC) pills containing 30 μg Estradiol in combination with levonogastrel. Gonal-F ® administration starting at dose 150 IU or 225 IU began on the first day of withdrawal bleeding after OC treatment. Cetrotide ® 0,25 mg was given daily from the evening of stimulation day (s-day) 5/morning of s-day 6 until the day before hCG administration. On the basis of the ultrasound scans performed on s-day9/10(s-day 9/10), and a calculation of follicular growth of 2mm per day, hCG was administered to trigger ovulation (when >2 follicle's ≥ 18 mm) were visualized.

Efficacy endpoint assessed included number of follicles ≥ 18 mm on s-day 9/10, total

number of vials of Cetrotide ® and ampoules of Gonal-F ® used, duration of Cetrotide ®and Gonal-F ® treatments, number of patients receiving hCG, patients undergoing oocyte retrieval, number of oocytes retrieved, reliability of prediction of day of oocyte retrieval, and pregnancy rate. Safety end-points were indicated and severity of adverse events.

Results

Preliminary results from 17 patents show that the mean number of follicles ≥ 18 mm on s-day 9/10 was 2,2. On the last day of Cetrotide® administration the mean number of follicles with diameters of ≤ 14 mm, 15 -17 mm and ≥18 mm were 2,7, 4,9 and 2,7 respectively. A median number of 24 ampoules of Gonal-F® equivalent to 75 IU were administered for 10,0 days, and daily injections of Cetrotide® 0,25 mg were administered for 5,7 days on average, respectively. All 17 women who received hCG had ovum pick up and embryo transfer. Overall, a mean number of 8,8 oocytes were retrieved and a mean of 2 embryos was transferred.

The pregnancy rate per attempt/cycle was 41%.The difference between predicted and actual day of OPU was 2 day on average. There as no cases of OHSS nor adverse events.

Conclusions

This is the first result of the use of Cetrotide® in COS cycles programmed by OCs. Overall, the stimulation results are similar to those observed in non-programmed cycles. Cetrotide® appears to be effective in OC programmed cycles ,is well tolerated and allows reliable prediction of the day of oocyte retrieval. Thus use of Cetrotide ® in programmed stimulation cycles represents another step towards well – tolerated , effective and convenient procedures in ART.

Cetrotide ® is the registered Trade Mark for the LHRH Antagonist cetrorelix.

The various embodiments which have been described herein intended to be representative and not limiting, as various changes and modifications can be made in the present invention without departing from the spirit and scope thereof.

Claims :

1.In the method of therapeutic management of infertility by programming of controlled ovarian stimulation (COS) and assisted reproductive procedures (ART) the improvement consisting of

a) suppression of premature ovulation with an LHRH-antagonist in controlled ovarian stimulation (COS) and assisted reproductive techniques (ART) with multiple follicle and oocyte development

b) programming the start of controlled ovarian stimulation (COS) by the administration of progestogen – only or combined oral contraceptive preparations

c) exogenous stimulation of the ovarian follicle growth

d) ovulation induction with HCG, native LHRH, LHRH-agonists or recombinant FSH

e) application of assisted reproduction techniques, especially of IVF, ICSI, GIFT, ZIFT or by intrauterine insemination by sperm injection.

2. The method of claim 1 wherein in order to perform oocyte pick up and fertilization procedures during Mondays to Fridays the start of a menstrual cycle and of COS are programmed.

3. The method of claim 1 wherein the programming of the start of the menstrual cycle and of controlled ovarian stimulation procedures oral contraceptives or progestogen-only containing preparations are given in the follicular phase, preferably starting at menstrual cycle day 1 or 2 or in the late luteal phase of the previous menstrual cycle.

4. The method of claim 1 wherein the intake of the last tablet will preferably be on a Mondays to Thursdays to obtain start of menstrual bleeding and of ovarian stimulation therapy on Fridays to Mondays and thereafter, oocyte pick up and further ART procedures can be scheduled and undertaken on Mondays to Thursdays.

5. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is cetrorelix.

6. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is teverelix.

7. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is ganirelix.

8. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is antide.

9. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the LHRH-antagonist is abarelix.

10. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by oral administration of progestogen preparations.

11. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by oral administration of progestogen- only containing contraceptives.

12. The method of therapeutic management of infertility by programming of COS and

ART procedures according to claim 1 in which the programming is achieved by oral administration of combined monophasic contraceptive preparations containing

ethinylestradiol and progestogen.

13. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is undertaken by oral administration of biphasic contraceptive preparations containing ethinylestradiol and progestogen.

14. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by oral administration of triphasic contraceptive preparations containing ethinylestradiol and progestogen.

15. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by oral administration of contraceptive preparations containing mestranol and progestogen.

16. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by the LHRH antagonist cetrorelix with a dosage of 0,5 to 10 mg administered during luteal phase .

17. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by the LHRH antagonist teverelix with a dosage of 0,5 to 10 mg administered during luteal phase .

18. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by

the LHRH antagonist ganirelix with a dosage of 0,5 to 10 mg administered during luteal phase.

19. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by the LHRH antagonist antide with a dosage of 0,5 to 10 mg administered during luteal phase.

20. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the programming is performed by the LHRH antagonist abarelix with a dosage of 0,5 to 10 mg administered during luteal phase .

21. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the stimulation is performed by administration of urinary or recombinant FSH or HMG, with or without recombinant LH.

22. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the ovarian stimulation is achieved with antioestrogens as for example clomiphene.

23. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the ovarian stimulation is achieved with the combination of antioestrogens with gonadotropins.

24. The method of therapeutic management of infertility by programming of COS and ART procedures according to claim 1 in which the ovarian stimulation is achieved with the combination of clomiphene with gonadotropins.